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# Hawaii's Neuromuscular Disease Biopsy Registry

## A Quarter-Century Compilation of Muscle Biopsy Diagnoses in Hawaii

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### Abstract

**Introduction:** The Department of Pathology at Straub Clinic & Hospital began using enzyme histochemical techniques to examine muscle biopsies in 1976 and has processed most of the muscle biopsies performed in Hawaii for the past 25 years. A Muscle Biopsy Registry of biopsy findings was established in 1992 and information concerning 1,230 biopsies during the period December 1976 to June, 2000 entered into the Registry's data base. The goal was to document data derived from biopsy-based diagnoses of neuromuscular diseases since none currently exists.

**Methods:** Muscle biopsies received in a fresh state in the Straub Pathology Department were processed utilizing a modern approach incorporating routine histological and enzyme histochemical staining techniques of frozen sections. One pathologist [LJL] documented findings and established diagnoses for all cases. Patient information, demographics and diagnoses were recorded utilizing a Microsoft Excel spreadsheet program.

**Results:** Data sorts conducted from the Registry's data base of 1,230 biopsies produced graphs and tables illustrating demographic statistics regarding diagnoses and findings in 1,044 different patients some of whom had multiple biopsies.

**Conclusions:** Hawaii's Neuromuscular Disease Biopsy Registry constitutes a compilation of a quarter-century of muscle biopsy-based diagnoses utilizing enzyme histochemical diagnostic techniques in pediatric and adult age groups, including specific diagnoses encountered in different ethnic groups. This information constitutes a benchmark for future epidemiologic studies, and a basis for comparison with data derived from clinical diagnoses and data derived from Death Certificates.

### Introduction

In 1976 the Department of Pathology at Straub Clinic & Hospital, Inc., switched from processing formalin-fixed, paraffin-embedded muscle biopsies with routine histological methods to a modern technique utilizing both routine histological as well as enzyme histochemical stains of frozen sections of fresh skeletal muscle biopsies. Straub's Department of Pathology has processed almost all muscle biopsies from within the State of Hawaii as well as some from the Pacific Basin during the 25 years of this review (1976 to 2000).

The compilation of all the muscle biopsy data enabled documentation of the prevalence and demographics of neuromuscular disease in Hawaii as diagnosed by muscle biopsy as opposed to diagnoses based solely on clinical grounds.

This is a unique situation since no other state has a centralized laboratory for processing the majority of muscle biopsies or a single registry of biopsy findings. In addition, Hawaii's ethnic diversity offers a unique opportunity for documenting the prevalence of muscle biopsy diagnoses in various racial and ethnic populations.

A Muscle Biopsy Registry was established to analyze the data. A computerized data base was developed with patient information and biopsy diagnoses obtained over the 25-year period between 1976 and 2000. Information from 1,044 different patients, some of whom had multiple biopsies totalling 1,230 biopsies, was compiled utilizing Microsoft's Excel spreadsheet program.

### Methods

Fresh, unfixed muscle biopsies received in isometric clamps were oriented and snap-frozen in isopentane, surrounded and cooled by liquid nitrogen. Six-micron thick, cryostat-cut frozen cross-sections were submitted for routine H&E, modified Gomoi trichrome, Oil Red O and PAS histological stains as well as NADH-TR and ATPase (at pH 9.4, 4.6 and 4.2) enzyme histochemical stains.

The remaining tissue was fixed in formalin and paraffin-embedded longitudinal sections stained with H&E.

In cases of suspected metabolic myopathies additional enzyme histochemical stains were performed, viz. acid phosphatase and phosphorylase.

When immunohistochemical staining techniques were developed additional stains for dystrophin and spectrin were performed in cases of muscular dystrophy.

Fluorescence microscopy was employed for Acridine Orange

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stained sections in cases of denervation.

Electron microscopy was performed in several cases of metabolic myopathies and lipid abnormalities.

All cases were read by one pathologist (LJL) and the histologic diagnosis assigned to one of 115 different diagnostic codes.

Additional codes for age, race, sex, biopsy site and other demographic data were entered into a Microsoft Excel spreadsheet.

## Results

Enzyme histochemical stains of frozen section preparations were required for establishing a histologic diagnosis in 76% of the biopsy specimens.

An XY scatterchart of the diagnostic categories from 1-115 along the vertical Y axis versus the case #1 to 1,230 (1976-2000) along the horizontal X axis is depicted in Chart 1.

Males comprised 57.8% of the patients and females 42.2%. The age and sex distribution and the distribution by sex in each decade is displayed in Charts 2 and 3 respectively.

The ethnic distribution within the Registry is depicted in Chart 4 by a pie-chart and the ethnic distribution of the biopsies compared with the State's population percentage of ethnic groups in Chart 5.

The most frequent pediatric diagnoses were: (1) Within normal limits, 15.3%; (2) Duchenne muscular dystrophy, 12.8%; (3) Infantile spinal muscular atrophy, 10.6%; (4) Non-diagnostic findings, 7.6%; (5) Polymyositis, 6%; and (6) Becker muscular dystrophy, 4.3%. These patients ranged from 0-19 years old and the above diagnoses comprised 56.6% of all the pediatric diagnoses in 235 patients. Chart 6 indicates the male/female ratio for the above 6 diagnoses.

The most frequent adult diagnoses were: (1) Changes secondary to neurogenic causation, 15.4%; (2) Within normal limits, 17%; (3) Polymyositis, 13.2%; (4) Type 2 atrophy, 13.1%; (5) Non-diagnostic findings, 10.3%; and (6) Motor neuron disease (ALS), 6.7%. The above diagnoses comprised 75.7% of all diagnoses in 995 adult patients (i.e. older than 19 years) and Chart 7 depicts the male/female ratio of the above 6 diagnoses.

"Changes secondary to neurogenic causation" includes a variety of entities manifested by neurogenic or re-innervation (and thus, indirectly, denervation) histologic changes but excluding all cases diagnosed as motor neuron disease (ALS). "Non-diagnostic" refers to biopsies with technical artifacts precluding accurate histologic assessment, autolytic/degenerative changes secondary to transport delays, or mild histologic abnormalities not specifically pathognomonic of either neurogenic or myopathic origin.

The distribution of the most common diagnoses in the 5 largest ethnic groups is depicted in the 5 pie-charts illustrated in Chart 8, and further tabulated in Tables 1 and 2.

Chart 9 depicts the percent of patients with ALS by ethnic group.

Chart 10 depicts the relative proportion of diagnostic groups in the Hawaii Muscular Dystrophy Association data for 500 patients compared with the same diagnoses in the Straub database of 1,230 patients.

## Discussion

Chart 1 indicates a relatively constant number of cases/year in several diagnostic groups including inflammatory myopathies, non-specific Type 2 atrophy and changes secondary to neurogenic

causation. Infrequent diagnoses scattered at random consist of metabolic myopathies, congenital muscular dystrophies, and toxic (ciguatera poisoning) myopathies.

Chart 2 indicates a preponderance of biopsies in males:females, most noticeable in the 20-29 year age group. This difference is also reflected in each of the three decades during which the data was collected (Chart 3).

Chart 4 indicates that the percentage of biopsies/ethnic groups was highest in Caucasians, followed by Japanese, Filipino, Chinese, Pacific Islander and Hawaiian, and Chart 5 compares these numbers with 1990 census data. The numbers for Japanese, Chinese, African-American, and Pacific Islanders approximated the proportion of these groups per the 1990 census data; Caucasians were over-represented and Filipinos and Hawaiians under-represented.

In the pediatric age group (0-19 years) Duchenne dystrophy was the most common diagnosis followed by infantile spinal muscular atrophy which was slightly more common in boys than girls. There were more cases of polymyositis in girls than boys (Chart 6).

In adults (Chart 7), changes due to neurogenic causation was the most common abnormality. The second commonest diagnosis was both polymyositis and Type 2 atrophy both of which were more frequent in women than men. Amyotrophic lateral sclerosis was more frequent in men.

Expressed as a percentage of diagnoses in each ethnic group, polymyositis occurred more frequently in Japanese, followed by Chinese, Filipinos, Caucasians and Pacific Islanders (Chart 8, Tables 1&2). Similarly, changes of neurogenic causation were commonest in Chinese, followed by Japanese, Pacific Islanders, Caucasians and Filipinos, and amyotrophic lateral sclerosis was most common in Chinese, followed by Caucasians, Filipinos, Japanese and Pacific Islanders.

There are only a few published reports regarding neuromuscular diseases in Hawaii<sup>1-5</sup>, and only one epidemiologic study<sup>6</sup>. The epidemiologic study published 30 years ago and four years prior to the start of our data collection, revealed an age and sex-adjusted incidence and mortality rate of amyotrophic lateral sclerosis (ALS) in Filipinos that was at least twice as high as any other ethnic group. The data was collected from the clinical records of the five largest hospitals and death certificates. However, neuropathologic material was available for histologic study in only one of the total of 42 cases of ALS diagnosed in the Filipino group over the 17-year period of data collection from 1952 to 1969.

Chart 9 depicts the number of cases of ALS in five ethnic groups and its percentage of all the diagnoses in each group. The numbers of ALS in Filipinos does not appear to support the previous epidemiologic conclusions. In addition, another study regarding the epidemiology of amyotrophic lateral sclerosis suggested that the excess among Filipinos in Hawaii was more a function of population age-distribution rather than a true ethnic difference<sup>7</sup>.

Chart 10 depicts the commonest eight diagnoses in 500 patients of the Hawaii Muscular Dystrophy Association (MDA) Registry, and the corresponding numbers in our data. The three most striking differences are the large number of Charcot-Marie-Tooth and myotonic dystrophy cases in the MDA data, and the large number of polymyositis cases in our data. The marked discrepancy in some diagnoses can be accounted for on the basis of clinical diagnoses (e.g. myotonic dystrophy) not requiring a muscle biopsy. Case

selection for inclusion in MDA programs probably accounts for some of the other differences.

## Acknowledgements

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Table 1

	Normal	Polymyositis	Neurogenic	Type 2 Atrophy	MND	Non-Dx	Other
Filipino	18 (18%)	10 (10%)	10 (10%)	11 (11%)	5 (5%)	8 (8%)	39 (39%)
Japanese	20 (8%)	40 (16%)	43 (17%)	27 (11%)	11 (4%)	21 (8%)	90 (36%)
White	72 (14%)	39 (8%)	60 (12%)	45 (9%)	35 (7%)	43 (8%)	220 (42%)
Pacific Islander	5 (13%)	2 (5%)	5 (13%)	7 (17%)	1 (3%)	2 (5%)	18 (44%)
Chinese	2 (4%)	6 (11%)	12 (23%)	14 (26%)	4 (8%)	1 (2%)	14 (26%)

Table 2

	Filipino	Japanese	White	Pacific Islander	Chineses
Normal	18%	8%	14%	13%	4%
Polymyositis	10%	16%	8%	5%	11%
Neurogenic	10%	17%	12%	13%	23%
Type 2 Atrophy	11%	11%	9%	17%	26%
MND	5%	4%	7%	3%	8%
Non - Dx	8%	8%	8%	5%	2%
Other	38%	36%	42%	44%	26%

Chart 1

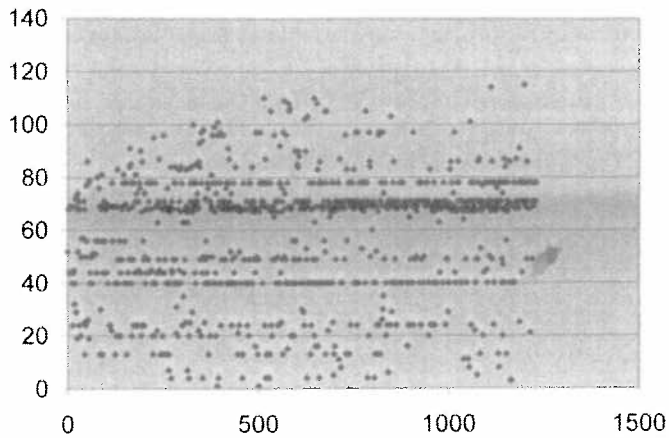


Chart 2

Age and Sex Distribution

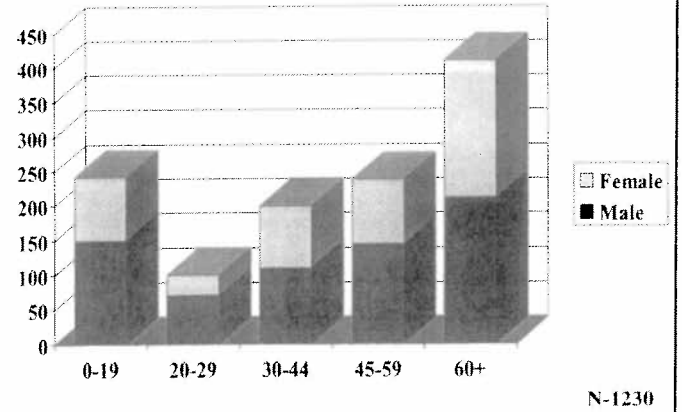


Chart 3

Distribution by Sex of Biopsies in Each Decade

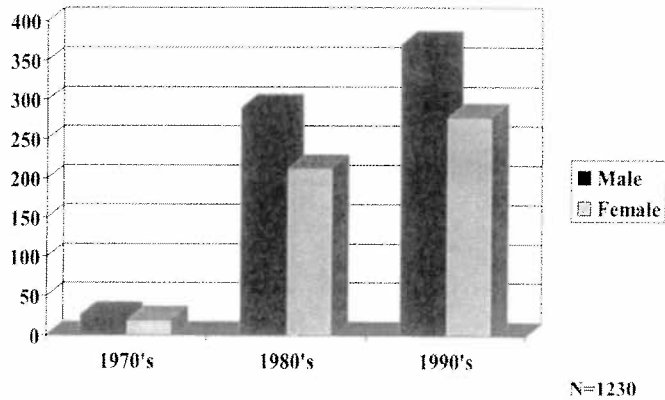


Chart 4

Ethnic Distribution within the Registry

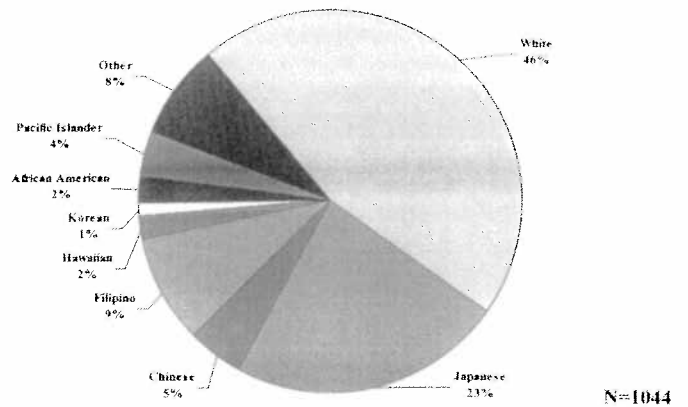


Chart 5

Ethnic Distribution

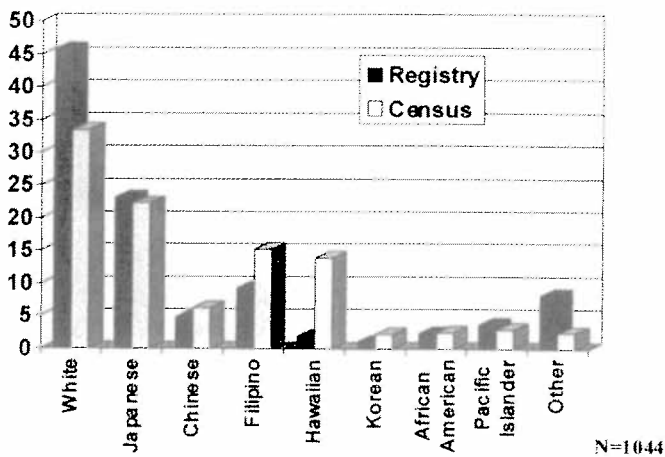


Chart 6

Most Frequent Pediatric Diagnoses

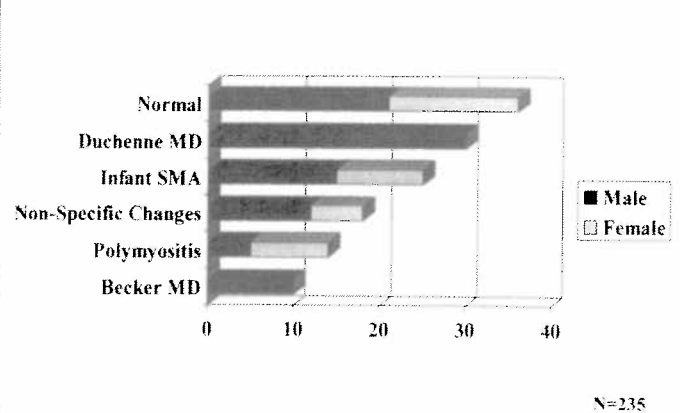


Chart 7

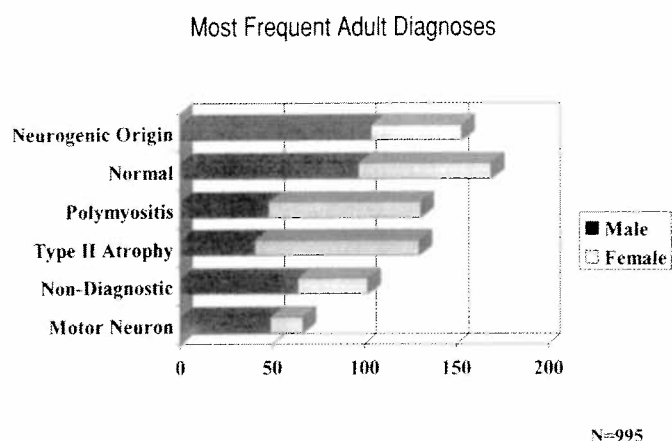


Chart 8

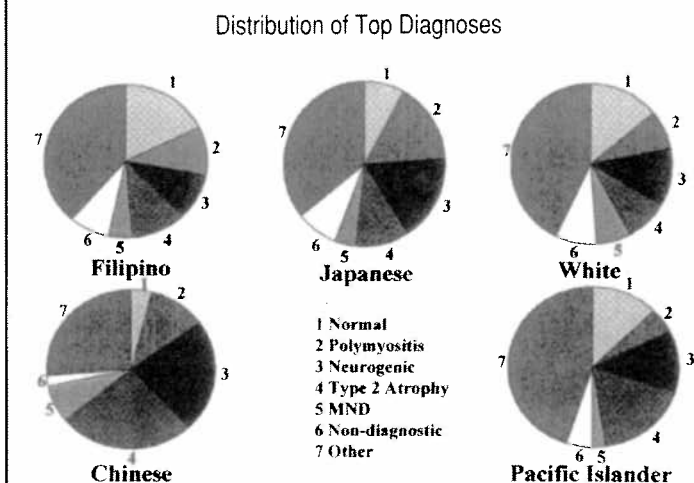


Chart 9

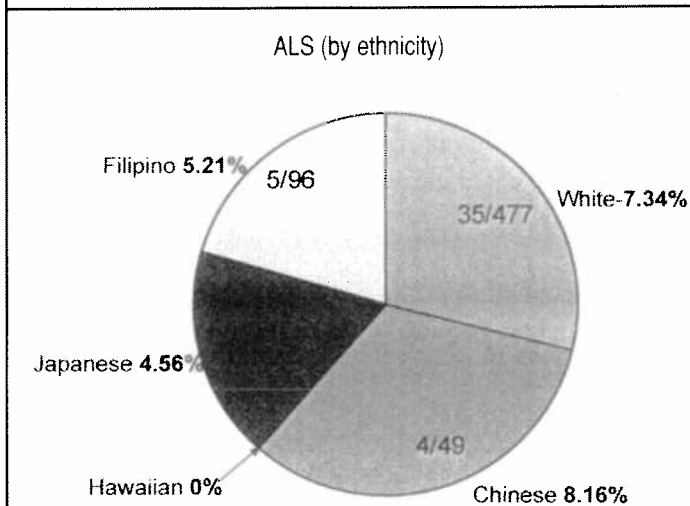
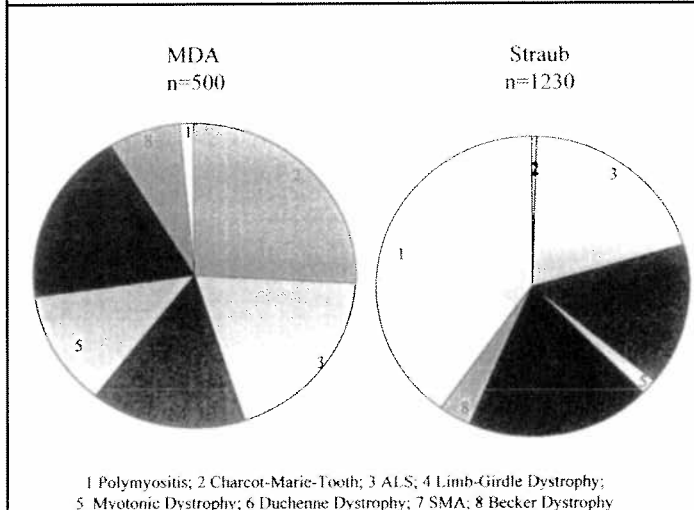


Chart 10



**Until there's a cure, there's the American Diabetes Association.**

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